BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

REMARKS

The Office Action has rejected Claims 7-17 under 35 U.S.C. §112, first paragraph, for allegedly being non-enabling. However, the Office Action has allowed Claims 1-6, 19-21 and 23-24.

Applicants have amended and added claims, which when considered with the comments hereinbelow, is deemed to place the present case in condition for allowance. Favorable consideration is respectfully submitted.

Applicants have cancelled Claims 7-17 without prejudice. Applicants have not abandoned the subject matter therein, but reserve the right to file one or more continuation applications directed thereto.

Claim 1 has been amended to correct the language to recite the Markush grouping in alternate form. Claim 3 has been amended to correct punctuation and to add an "and" prior to the last chemical structure. In addition, Claims 25 and 26 have been added to the application. Support thereof is found in original Claims 8 and 9.

No new matter has been added to the application.

In support of the rejection of Claims 7-17, under 35 U.S.C. §112, first paragraph, the Office Action admitted that the specification is enabling for treating ischemic diseases. However, it alleges that the application is not enabling for the prophylactic and/or treatment of disorders related to the neuronal damage of the central nervous system. It alleges that it does not believe that the compounds of the present invention are useful for the prophylaxis and treatment of disorders related to the neuronal damage of the central nervous system.

Applicants agree that the application is enabling for treating ischemic diseases. However applicants respectfully submit that the application is enabling for the prophylaxis and treatment of disorders related to the neuronal damage of the central nervous system. Applicants disagree that the remaining scope of the claimed subject matter is not enabled. Applicants reiterate the comments provided in the Response dated November 15, 2002 and incorporate the same by reference, as if fully set forth herein. Applicants have shown that the Office Action has not made out a prima facie case for it has not provided any evidence contradicting the statements in the application that the compounds of the present invention have the requisite utility, in accordance with the holding In re Marzucchi, 439 F2d. 220, 224, 169 USPQ 367, 370 (CCPA).

The Office Action cites Vajda. But Vadja does not support the position of the Office Action.

On any balanced reading Vajda supports the view that common pathways are important in a wide variety of neurological diseases, that glutamate triggers excitotoxicity and NMDA receptors are involved. It is true that Vajda also suggests that known drugs may offer some potential in neurological diseases and that the use of known drugs may save on the need to develop new drugs. However, this latter point is of little relevance with respect to the present invention. Moreover, Vajda does not state, as the Office Action has alleged, that compounds which are NMDA antagonists and sodium channel blockers are not useful for the treatment or prophylaxis of neurological disorders.

Further applicants have previously enclosed various publications which support the role of NMDA antagonists and voltage-sensitive sodium channel blockers in a broad range of neurological indications. The publications include:

1. U.S. Patent No. 6,376,530 to Claiborne, et al., which describes and claims a series of NMDA receptor antagonists and the therapeutic use of such compounds. In fact, the background in Column 1 and 2 provides a useful overview of the potential therapeutic indications for NMDA antagonists.

2. U.S. Patent No. 6,063,774 to Nikam, which describes a group of NMDA receptor antagonists and methods of treatment using such compounds. A ligand binding assay was used to determine the NMDA receptor binding properties of the compounds. Claim 8 thereof is directed to a method for the treatment of neurodegenerative disorders and then lists numerous disorders which overlap substantially with those of the present invention.

3. U.S. Patent No. 6,245,777 to Grauert, et al. This patent describes and claims a group of compounds which are blockers of the voltage dependent sodium channel and the therapeutic use of such compounds. Column 2 lines 42-51 lists various diseases and conditions which may be treated with sodium channel antagonists. Claims 15-20 thereof are drawn to methods of treating disorders caused by overstimulation of voltage-dependent sodium channel using the sodium channel antagonists described therein.

Column 2 lines 52-55 describes a ligand binding assay for determining antagonism of the test compounds at voltage-sensitive sodium channels using labeled batrachotoxin (BTX). Column 2 lines 63-67 describe an assay to determine the blocking of veratridine-induced activity; veratridine is a toxin which opens the sodium channel.

4. U.S. Patent Nos. 6,355,652 and 6, 387,921 to Grauert et al. These related patents are similar to 6,245,777 discussed above, except that the claims also

include Alzheimer's disease as a further disease which may reasonably be expected to be treated with a voltage dependent sodium channel antagonist.

Again assays involving BTX displacement and blockage of veratridine-induced activity were used to demonstrate the sodium channel blocking properties of the compounds.

The above noted U.S. patents provide a useful overview of the state of the art with respect to the role of NMDA receptor antagonists and voltage sensitive sodium channel antagonists in treating various neurological diseases and conditions. They also provide an indication of assay systems which may be used to determine NMDA receptor activity and activity at voltage sensitive sodium channels. Some of the assays used to define the activity of the compounds of the present invention are substantially similar to the assay used in the cited patents. For example, the NMDA receptor activity of the compounds of the present application is assessed in a ligand binding assay using [^{3}H]-ifenprodil, the exact ligand used in U.S. Patent No. 6,376,530. Antagonism at voltage sensitive sodium channels was assessed in the present invention in both a labeled batrachotoxin binding assay and an assay to block veratridine-induced activation of sodium channels. These very same types of assays are used in U.S. Patent No. 6,245,777, U.S. Patent No. 6,355,652 and U.S. Patent No. 6,387,921 to assay activity.

In summary, it is clear that both the NMDA receptor and voltage sensitive sodium channels are well established targets for intervention in neurological conditions and diseases. In view of the common pathways implicated in many of these diseases and conditions, antagonists of either of these targets are considered by those skilled in the art to be useful across a broad therapeutic spectrum. When compared with the state of the

art it is clear that the assays used in the present application are accepted as being reasonably predictive of activity against these targets.

Further with respect to the comments of the Office Action on page 3 that there no known drugs which successfully reverse the course of disease, such as Alzheimer's diseases, Parkinson's disease ALS, it is submitted that treatment does not require the reversal of the course of a disease or the cure of that disease. There are of course treatments available for these diseases today including Alzheimer's disease; for example Aricept, Exelon and Reminyl are all approved therapeutics. Moreover, it is noted that the cited patents include methods of treatment claims to a broad range of disorders including diseases such as Alzheimer's disease, Parkinson's disease, ALS, and the like. Thus, it is apparent that there is precedent for the United States Patent and Trademark Office to permit the claims to recite the use of compounds for the treatment and/or prophylaxis of these diseases.

Case law has held that there are various factors in determining the enablement question and these are discussed in In re Wands, 858 F2d 731, 8 USPQ2d 1400. Applying the factors of In re Wands, to the subject matter in Claims 7-17, it is respectfully submitted that a skilled artisan would conclude that the present application is enabling for all of the embodiments claimed therein.

1. The nature of the invention: It relates, inter alia, to the therapeutic use of compounds of formula (1) in treating diseases that relate to the neuronal damage of the central nervous system relating to the inhibition of the NMDA receptors and voltage sensitive sodium channels.

2. The state of the prior art: The prior art of record show that both the NMDA receptor and voltages sensitive sodium channel are well established targets for intervention regarding neurological conditions.

3. The predictability thereof: Based upon the acceptance of the scientific community, as evidenced hereinabove, regarding the inhibitory effect of NMDA receptors and voltage sodium sensitive channels and the use of compounds effecting these inhibitory effects, and based upon the antagonistic effect of the compounds of the present invention on NMDA receptor and voltage sensitive sodium channels, it is respectfully submitted that the utility thereof is quite predictable.

4. The amount of direction and (5) working examples: The specification provides adequate direction and guidance for the use of the compounds of the present invention for the treatment of the various diseases described in the specification. See page 15, line 15 et seq. Case law has held that working examples are not required if the specification is otherwise enabling. See In re Borkowski, 422 F2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). As described hereinabove, it is so enabling.

Thus, the specification provides adequate guidance for one of ordinary skill in the art to practice the present invention without undue experimentation.

6. The breadth of the claims: The claims are not overly broad but are commensurate in scope with the enabling disclosure. The claims are no broader than the teachings in the specification.

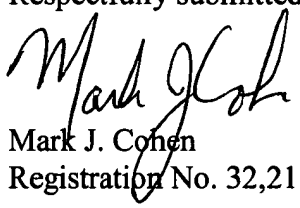
7. The quantity of experimentation. Based upon the teaching in the specification, it is respectfully submitted that the present invention can be practiced without undue experimentation.

Thus, applicants believe that the claimed invention as originally filed is enabled. Nevertheless, to advance prosecution, applicants have cancelled Claims 7-18 without prejudice. However, the cancellation of these claims is not based on issues relating to the patentability of the claim; it is based on expediency.

It is therefore submitted that the rejection of Claims 7-17 under 35 U.S.C, §112, is overcome; withdrawal thereof is respectfully requested.

In view of the remarks hereinabove, it is respectfully submitted that the present case is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



Mark J. Cohen
Registration No. 32,211

Scully, Scott, Murphy & Presser
400 Garden City Plaza
Garden City, New York 11530
(516) 742-4343

MJC:lf